Remarks

A request for a three (3) month extension of time from November 10, 2005 to February 10, 2005 is being filed herewith. In the event that such request should become separated from this paper, the required fee for such extension of time is hereby authorized to be charged to Deposit Account No. 10-0750 of Johnson & Johnson.

Claims 18-26 are in the case. Claims 1-17 were previously cancelled. Claims 18-26 stand rejected.

Please cancel Claims 18-26 without prejudice to the later filing by Applicants of applications directed to the cancelled subject matter.

Claim Rejections

The claim rejections in the *Office Action* are rendered moot by the cancellation of Claims 18-26.

New Claims

Please add new claims 27-46. Claims 27-31 are directed to methods for inhibiting platelet aggregation. The method of Claim 27 comprises two steps. In the first step, a thrombin receptor antagonist is selected from the broad genus disclosed on page 3, line 7 to page 4, line 13 of the specification as filed. This genus comprises both thrombin receptor antagonists and agonists. The skilled artisan is provided with the means for selecting antagonists from agonists in the specification as filed. First, Tables 1 and 2, at pages 9 and 12 of the specification respectively, provide examples of agonists and antagonists, respectively. Second, the thrombin receptor assay in Example 4 and the platelet aggregation assay at Example 5 provide convenient means of testing a desired compound for antagonistic versus agonist thrombin receptor binding activity and inhibition versus induction of platelet aggregation. Thus, the selection step is inherent in the disclosure as filed. In the second step, a therapeutically effective amount of the selected compound is administered to the subject. The skilled practitioner using standard clinical practices can determine the therapeutically effective amount of a selected

compound. Table 2 of the specification as filed supports the scope of Claim 28. The compounds of Claim 29 were selected from the list on page 13 by reference to Table 1 and 2 to select the three particularly preferred compounds having antagonist activity.

Claims 32-36 are similarly directed to methods for inducing platelet aggregation. Support for these claims may be found in the specification as filed as described in the paragraph herein above.

Claims 37- 41 are directed to a method of treating a platelet-mediated thrombotic disorder selected from the group consisting of myocardial infarction, stroke, angina, and ischemic attacks in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula I. Support for the scope of compounds encompassed by these claims may be found in the specification as filed as described herein above. The platelet-mediated thrombotic disorders are selected from the list of disorders on page 3, lines 1 and 2 of the specification as filed.

As discussed in the Declaration of Claudia Derian, attached hereto at Exhibit A, it is well known that platelets play a major role in promoting vascular occlusion via platelet aggregation and subsequent thrombosis culminating in clinical disorders such as arterial thrombosis, venous thrombosis, acute myocardial infarction, ischemic attacks, angina, stroke and reocclusion following interventions such as thrombolytic therapy or angioplasty (Chesebro et al., *Circulation,* **86**, [suppIII] 100-110, 1992; Verstraete and Zoldhelyi, *Drugs*, **49**, 856-884, 1995; White, HD, *Am Heart J*, **138**, S570-S576, 1999; Weksler, *Cerebrovasc Dis*, **10**, 41-48, 2000, attached hereto in Exhibit B). Several platelet aggregation inhibitors have been tested *in vitro* and *in vivo* and have now been developed as marketed products for the treatments of thrombotic disorders. For example, clopidogrel (e.g., **Plavix®**), inhibits platelet aggregation by blocking the ADP receptor on platelets (Verstraete and Zoldhelyi, *Drugs*, **49**, 856-884,1995, attached hereto in Exhibit B). Clopidogrel can inhibit platelet aggregation in animal models preventing thrombis formation. Based on these studies, it has received marketing approval to treat myocardial infarction, stroke, vascular occlusive diseases such as peripheral arterial disease and angina in patients being treated with cornonary interventions, such as angioplasties,

including stents. Another example includes the class of fibrinogen receptor antagonists known as glycoprotein IIB/IIIa antagonists. This protein is expressed on the surface of platelets and is the common pathway by which fibrinogen binds and induces platelet aggregation. Blockage of this receptor prevents platelet aggregation. Compounds have been described in the literature that bind this receptor *in vitro*, in animal models of thrombosis, and in clinical studies. Several compounds which inhibit platelet aggregation are presently marketed for the treatment of thrombosis related disorders. For example, the following compounds are currently approved and marketed products: **ReoPro®** (abciximab), **Integrilin®** and **Aggrastat®** (tirofiban). In general, all three agents are approved to treat acute coronary syndromes (unstable angina), to be used during interventional procedures such as angioplasty (Mousa, *Drug Discovery Today*, **4,** 552-561, 1999, attached hereto in Exhibit B). Declaration of Claudia Derian at paragraphs 3-5.

In vivo studies of clopidogrel in a guinea pig model of thrombosis were conducted in Johnson & Johnson's laboratories. Clopidogrel significantly prolonged the time to occlusion compared to vehicle treated animals in a model where a thrombus was generated by endothelial injury (Fig. 1). Furthermore, a small molecule PAR-1 antagonist, which represents a new mechanism for inhibiting platelet aggregation *in vitro*, was shown to inhibit platelet aggregation *ex vivo* in guinea pigs (Andrade-Gordon et al., J Pharmacol Exp Ther, 298, 34-42; noted on pg. 36-37 and Fig 2, attached hereto in Exhibit B). Moreover, it has been demonstrated that the PAR-1 antagonist inhibited thrombosis in both a guinea pig model of carotid injury (Andrade-Gordon et al., *ibid*, *see* Fig 4 therein) and most importantly in a primate model (Derian et al, J Pharmacol Exp Ther, 304, 855-861; *see* Figs. 3, 4 and 6 therein, attached hereto in Exhibit B). These results are consistent with data known in the art which demonstrate that agents which inhibit platelet aggregation and prevent *in vivo* platelet thrombus are clinically efficacious for treating platelet dependent disorders. Declaration of Claudia Derian at paragraph 6.

Thus, in light of the state of the art at the time the present application was filed and the disclosure in the specification as filed, one of ordinary skill in art would understand how to use the compounds of the present application for the treatment of platelet-mediated thrombic disorders such as such as arterial thrombosis, venous thrombosis, acute myocardial infarction, ischemic attacks, angina, stroke and reocclusion following interventions such as thrombolytic therapy or angioplasty. Declaration of Claudia Derian at paragraph 7.

Claims 42-46 are directed to a method of treating restenosis in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula I. Support for the scope of compounds encompassed by these claims may be found in the specification as filed as described herein above. Support for restenosis is found on page 3, line 1 of the specification as filed.

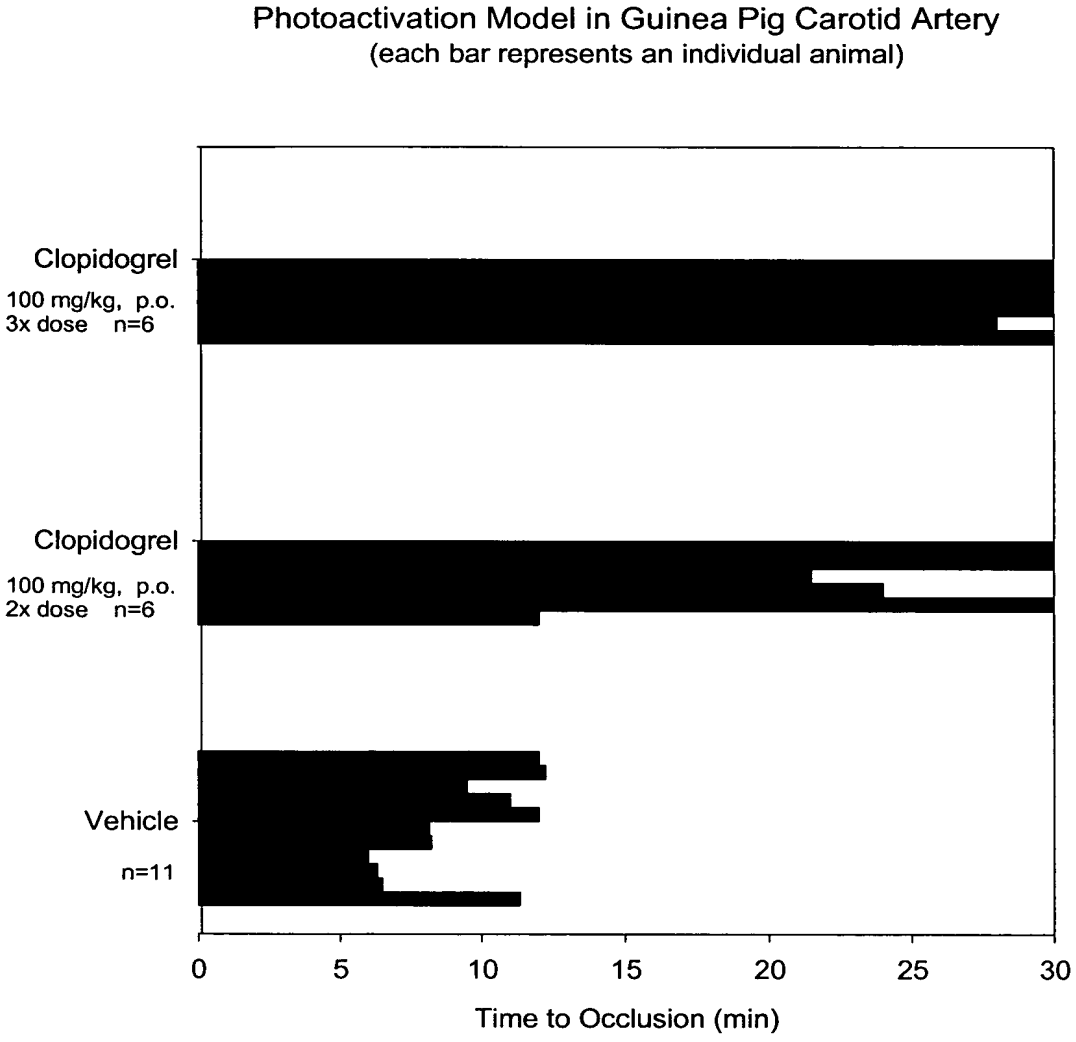
As discussed in the Declaration of Claudia Derian at paragraphs 8 and 9, the pathophysiological processes that lead to restenosis of a blood vessel are not fully defined, however it is clear that injury to the blood vessel during clinical procedures, such as angioplasty, leads to processes including platelet aggregation, injury to the vessel causing inflammation, and induction of vascular cell proliferation (Linde and Strauss, *Expert Opin Emerging Drugs*, **6**, 281-301, 2001, attached hereto in Exhibit B). Restenosis may be prevented from occurring by inhibiting platelets from aggregating at the vessel wall surface and releasing their cellular contents. This clinical syndrome was apparent in early cases of coronary catheter injury and stent placement (Ischinger, *Am J Cardiol*, **82**; 25L-28L. 1998; Schwartz, *Am J Cardiol*, **81**, 14E-17E, 1998, attached hereto in Exhibit B).

The state of the art medical procedure for treating postinterventional vascular reocclusion in patients is to administer antithrombotic agents, thus preventing the platelet aggregation and the release of potential agents to stimulate smooth muscle proliferation, (i.e. platelet derived growth factor) and to implant drug coated stents. Declaration of Claudia Derian at paragraph 9. Agents used clinically as antithrombotic agents include **Plavix®**, **Aggrastat®** and **ReoPro®**. Directly or indirectly preventing the stimulation of

cell proliferation at the site of injury leads to the prevention of restenosis (Linde and Strauss, *ibid.*). In addition to indirectly affecting the proliferation of vascular smooth muscle cells through anti-platelet agents, more direct agents such as Sirolimus (rapamycin) or Taxol, have been shown to inhibit the proliferation of vascular smooth muscle cells (Marx, et al., *Circ Res.*, **76**, 412-417, 1995; Sollott et al., *J Clin Invest*, **95**, 1896-1876, 1995; Suzuki et al., *Circulation*, **104**:1188-1193, 2001). Both these agents are utilized clinically to prevent post-stent restenosis based on their ability to prevent vascular smooth muscle dependent proliferation.

A thrombin receptor antagonist for PAR-1, which is expressed on both platelets and vascular smooth muscle cells, has been shown to inhibit restenosis by inhibiting both *in vitro* vascular smooth muscle proliferation and platelet aggregation. *See* Andrade-Gordon et al. (2001) pp. 35 and 36. Inhibition of restenosis was demonstrated in an *in vivo* rat restenosis model as shown in Fig. 6 by histology and in Table 1 by quantitative assessment. These results are consistent with previously described data demonstrating the role of inhibiting vascular smooth muscle proliferation to provide clinically efficacious results for prevention of restenosis. Declaration of Claudia Derian at paragraph 10.

Figure 1: Inhibitory effects of Clopidogrel on thrombus formation in a guinea pig carotid thrombosis model. Each bar is an individual guinea pig response over 30 minutes. The dark bar shows the duration of patency in minutes following photoactivation with Rose Bengal dye. Guinea pigs were orally dosed for either 2 or 3 days with clopidogrel (100 mg/kg)



Applicants believe that this reply is a full and complete response to the pending *Office Action*, and that new Claims 27-46 are now in condition for allowance. Applicants respectfully request the issuance of a timely Notice of Allowance in this case.

Respectfully Submitted,

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